**REMARKS**

In response to the Non-Compliant Amendment set forth in the Office Action of May 1, 2009, Applicant hereby submits additional remarks to be responsive to each of the 35 U.S.C. 112, first paragraph, rejections.

*New Remarks to Rejections under 35 U.S.C. §112*

The Examiner rejects claims 43-46 and 48 under 35 U.S.C. §112 as as containing subject matter not described in the specification. Specifically, the Examiner states the specification only provides enabling disclosures for vectors comprising the WPRE. Amended claim 43 recites *"woodchuck post-transcriptional regulatory element"* and is enabled and patentable. Since claim 46 depends on claim 43, claim 46 is also patentable for at least the same reasons as stated above for claim 43. Moreover, the cancellation of claims 44-45 and 48 have been rendered the 112, first paragraph, rejections moot.

Applicants' response to the remaining grounds for rejection have not changed and reference is made to the January 13, 2009, and October 17, 2008, submissions for the remarks. For convenience, the response has been copied below.

*The Claims*

Claim 43 has been amended. Claims 44,45,47 and 48 have been cancelled. New claims 49-55 have been presented. Support for the new claims can be found throughout the specification, especially in Examples 1-8.

*Rejection under 35 U.S.C. §112*

The Examiner has rejected pending claims 43-48 under 35 U.S.C. §112 as failing to meet the written description requirement. The claims previously recited "a post-transcriptional regulatory element". The Examiner contends that although the application recites the use of post-transcriptional regulatory elements, the claims "encompass a genus of genetic elements that are not described." According to the Examiner, the claims "cover the use of a genus of genetic elements,

while providing a description of only a single post-transcriptional regulatory element.", namely the WPRE regulatory element. Although Applicants maintain their prior position and restate the relevance of the Schambach et al. reference as an indication of the level of ordinary skill in the art, Applicants have amended claim 43 to recite the WPRE regulatory element in order to advance prosecution.

*Rejection under 35 U.S.C. §103.*

**Geoffroy et al. is not proper prior art**

The Examiner has rejected claims 43-48 under 35 U.S.C. 103(a) as being unpatentable over U.S. 2002/0028212 (Geoffroy et al.), in view of Loeb et al. This rejection is improper. The Geoffroy reference is not prior art under 35 USC § 102.

Geoffrey et al is a published patent application. As of the date of this response no patent has issued based on this application. Geoffrey et al. published in March 7, 2002. The application appears to be a National Stage Entry of a PCT application filed on Mach 21, 1995.

A 35 U.S.C. § 103 rejection must be based on 35 U.S.C. §§ 102(a), 102(b), 102(e), etc. depending on the type of prior art reference used and its publication or issue date. (MPEP 2141.01).

U.S. patent application publications are prior art under 35 U.S.C. 102(a) and 102(b) as of the publication date. Under amended 35 U.S.C 102(e)(1), a U.S. patent application publication under 35 U.S.C. 122(b) is considered to be prior art as of the *earliest effective U.S. filing date of the published application,* (MPEP 901.03), except where the US application is based on an International Application (IA) filed *before November 29, 2000.* Where the IA is either not published in English or did not designate the US the reference is not prior art under 102(e) and can only be prior art under 35 USC 102(a) or 102(b).

It is well established that the effective filing date of a CIP is the date that the relevant material first appears in the application. (MPEP 2136.02) ("subject matter not included in the parent… can only be used when that subject matter become public.")

The Geoffroy et al. reference published (March 7, 2002), AFTER the filing date of the parent application (May 23, 2001) and provisional application (Ser. .No. 60/206,281, filed May 23, 2000) upon which this application and the parent application take priority. The claimed subject matter, namely a vector for expressing GAD65 in cells of the central nervous system comprising a tissue specific promoter operably linked to a nucleotide sequence encoding GAD65 and the WPRE post-transcriptional regulatory element is disclosed throughout the instant application (See, e.g., paragraph [0023]). The same description also appears in the PARENT application, Ser. No. 09/863,179, that was filed on May 23, 2001 (See, e.g., Column 3 line 66-Col. 4, line 3 of U.S. Pat. No. 6,780,409). Thereby establishing an effective filing date of the material in the instant application of on or before May 23, 2001. As such, the Geoffroy et al. reference cannot be prior art under 35 U.S.C. §§ 102(a) or 102(b).

As no patent has issued, Applicants assume that the Examiner is citing the reference as prior art under 35 U.S.C. § 102(e), namely, as "an application for patent, published under section 122(b) by another filed in the United States before the invention by the applicant for patent" (35 U.S.C. § 102(e)(1)).

As mentioned above, the Geoffroy et al. is based on an International Application that was filed on March 21, 1995. The IA, PCT/FR95/00342 appears to have published as WO 95/25805 on September 28, 1995. The published application is in French. As the IA is not in English, the published US application US 2002/0028212 that takes priority from the IA cannot be prior art under 102(e).

The cited References do not render obvious the claimed invention

Claim 43 as amended recites a vector for expression of GAD65 in cells of the central nervous system of a subject comprising: (a) AAV, (b) a tissue specific promoter operably linked to a nucleotide sequence encoding GAD65; and (c) the WPRE regulatory element.

The cited art does not disclose or suggest such a construct with the stated functionality.

First, we note that the Loeb et al reference discloses the use of an AAV-WPRE vector to transduce (a) 293 cells and (b) primary human fibroblasts in culture. The authors note on page 2303 that these two experiments in combination only allow the conclusion that "WPRE can function to enhance gene expression in a heterologous viral context in *cultured primary human cells*" (emphasis added). We note that (a) none of the cells disclosed in Loeb et al. were neural cells, which by their nature are very different than 293 cells or primary human fibroblasts ; (b) there was no indication that the WPRE regulatory element would function properly *in vivo; and* (c) there was no indication that the WPRE would function appropriately in conjunction with any promoter let alone the specific promoters disclosed in the instant application .

Second, the Examiner relies on Geoffroy for the proposition that:

> Geoffroy et al. disclose the construction of an adenovirus vector comprising a gene encoding GAD67 under the control of RSV-LTR (see Example 1). The reference further discloses that the RSV-LTR promoter is advantageous for the expression of GAD in nerve cells and that the neuron-specific enolase promoter is particularly advantageous for expression in nerve cells (paragraph 0028). The reference further discloses that AAV vectors are particularly useful because they integrate into the genome of cells, are not involved in pathologies in man, and infect a broad spectrum of cells (paragraphs 0023-0024 Geoffroy et al. further disclose that recombinant vectors encoding GAD are useful for treating and preventing degenerative neurological diseases (abstract and throughout specification).

The Examiner seems to imply that Geoffroy et al. discloses vector(s) capable of transfecting cells of the central nervous system of a subject namely primary neural cells. This is not the case.

First, Applicants note that neither of the vectors of Geoffroy that were used for transfection appear to have include a gene encoding both GAD67 (let alone GAD65) and the RSV-LTR. The RSV-LTR construct (pLTR IX GAD67) of Example 1 was only successful in transfecting 293 cells in culture. (See Example 2 of Geoffroy). Example 5, which purports to describe the *in vivo* transfer of GAD 67 by a recombinant adenovirus is (a) purely prospective; and (b) discloses the use of AD-

GAD67, a vector that does not appear to contain the RSV-LTR. The final construct disclosed by Geoffroy et al. (pMoMuLV-GAD) also does not appear to carry the RSV-LTR promoter.

Second, Applicants note that the only Example(s) that show any infection of "neural" cells are Examples 9-11. Example 9 discloses the use of retroviral supernatants obtained from Ψ-2 cells that were co-transfected with the plasmid pMoMuLV-GAD; the Ψ-2 cells having a provirus expressing all the retroviral functions required for encapsulation of the retroviral transcript. This supernatant was then used to infect two rat neural progenitor cell lines HiB5 and ST14A, derived from embryonic hippocampus and striatum primordium. These cells were then *transplanted* (see Example 11) into Sprague-Dawley rats. Geoffroy et al. then found that GAD-specifc immunolabeling was limited to the transplanted cells. In short, Geoffroy et al. were *unable* to transfect primary cells of the CNS of a subject, only embryonic progenitor cells in culture, that were then transplanted into the subject.

Applicants therefore submit that the cited references do not render obvious the claimed invention and believe that the claims as they currently stand are allowable. As such allowance is respectfully requested.

## CONCLUSION

Applicants believe that the presently pending claims are in immediate condition for allowance and allowance is therefore respectfully requested. However, should any issues remain, the Examiner is urged to telephone the undersigned Attorney for Applicant in the event that such a communication is deemed to expedite allowance of this application.

Dated: May 28, 2009

Respectfully submitted,

By: _____
George A. Xylis
Registration No.: 38,664
NUTTER MCCLENNEN & FISH LLP
World Trade Center West
155 Seaport Boulevard
Boston, Massachusetts 02210-2604
(617)439-2746
(617) 310-9746 (FAX)
Attorney for Applicants

1826948.1